



Case report

Escherichia Coli bacteremia and rapidly progressive cellulitis in a child with newly diagnosed nephrotic syndrome

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ABSTRACT

Nephrotic syndrome (NS) in children is associated with spontaneous bacterial infections, including peritonitis as well as cellulitis secondary to chronic third-spacing of intracellular fluid. Typical pathogens that cause cellulitis in these patients are gram-positive bacteria whereas gram-negative organisms are uncommon. We report a case of *Escherichia coli* bacteremia with associated rapidly progressive cellulitis in an 11-year-old child with newly diagnosed NS, who had only recently started steroid therapy. Our case highlights the multifactorial effects of NS on the immune system that result in a predisposition towards infection. It also underscores the importance of a broad approach to neuro-atypical children with common clinical complaints.

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Introduction

Nephrotic syndrome (NS) is a clinical syndrome characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. NS results from multiple underlying etiologies, which influence patients' responsiveness to treatment. Children with NS are at risk for complications, particularly infection because of the pathophysiology of NS and the use of immunosuppression therapy in its treatment [1]. The case presented demonstrates an atypical microbiological etiology of a common pediatric diagnosis, and highlights how the underlying disease process in conjunction with initiation of therapy may have contributed to infection.

Case report

An 11-year-old boy with a past history of nonverbal autism spectrum disorder (ASD), epilepsy, and congenital ventriculomegaly presented to his pediatrician with one week of abdominal and lower extremity swelling. Work-up was consistent with NS, for which he was referred to pediatric nephrology and then started on oral prednisolone 30 mg twice/day (approximately 1.2 mg/kg/day). His other home medications included lamotrigine, levetiracetam, vitamin D, and famotidine.

One week later, he presented to the emergency department after having a seizure lasting several minutes that required intervention with rectal diazepam; his prior seizures had always been brief and never required benzodiazepines. After a brief post-ictal period, he appeared to have a new-onset wide-based gait. Vital signs were within normal limits for age. Examination revealed a rash at the anterior proximal aspect of his left thigh. The rash was targetoid in appearance with an intense, non-blanching erythematous outline and satellite petechiae (Fig.1). There was also symmetric pitting edema in the lower extremities extending to the hips with prominent scrotal edema.

Initial laboratory data was notable for WBC count of $13.4 \times 10^9/L$ (81 % neutrophils), albumin 1.4 g/dL, calcium 7.0 mg/dL (9.1 when corrected for albumin), and CRP of 130 mg/L; urinalysis with protein of 100 mg/dL, 1 WBC/hpf, negative leukocyte esterase, and negative nitrites; and a urine protein-to-creatinine ratio >3.85. Creatinine was 0.3 mg/dL, which was unchanged from the week prior.

Within several hours of admission, confluent erythema and warmth extended superiorly to the abdomen and distally down the left lower extremity, eventually reaching the ankle. Given the rapidly progressive nature of the rash and evolving cellulitic appearance, blood cultures were drawn and the patient was started on intravenous cefazolin while discontinuing prednisolone because of the concern for active infection.

The blood culture began growing gram-negative rods within 16 h, for which therapy was changed from cefazolin to piperacillin-tazobactam. Speciation later revealed *Escherichia coli* with sensitivity to all tested antibiotics, including ampicillin,

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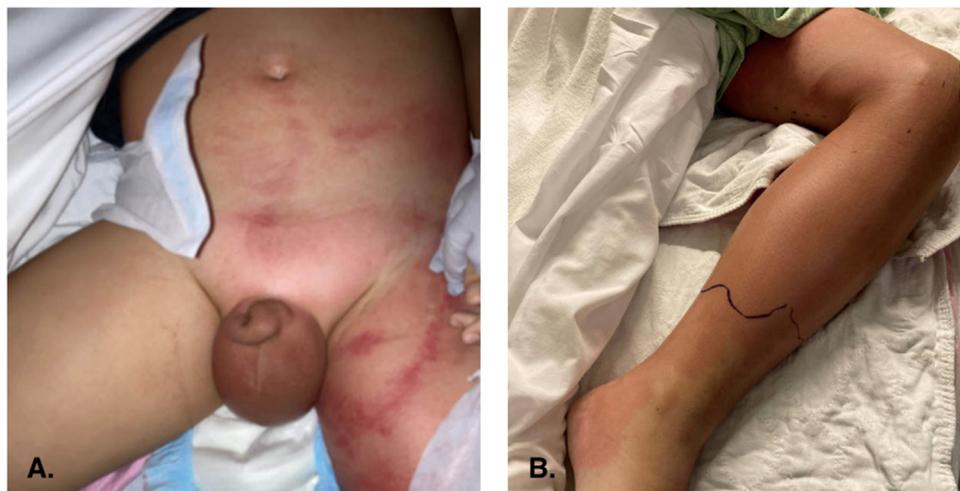


Fig. 1. Evolution of cellulitis. 1A Targetoid erythematous skin lesion with scrotal and abdominal edema present 1B. Extension of cellulitis less than 24 h from initial blood culture.

ceftriaxone, cefepime, fluoroquinolones, trimethoprim-sulfamethoxazole, and carbapenems. He transitioned to ceftriaxone and later, with ongoing clinical improvement, was discharged home on cefdinir to complete a total 2-week course of antibiotics for treatment of bacteremia and cellulitis.

Additional work-up during his hospitalization included a venous ultrasound of the left leg, ordered because of the association of NS with hypercoagulation [1], which showed no evidence of deep venous thrombosis. An abdominal ultrasound showed no abnormalities or focal sources of enteric bacteremia, such as an abscess or enteritis.

The patient returned to the hospital two weeks later with tender erythema and swelling again at the proximal aspect of the left thigh. MRI revealed myositis and fasciitis of the left hemipelvis with small non-drainable fluid collections interposed between the left obturator internus muscle and the left ischium. Blood cultures had no growth. His symptoms improved on cefazolin, after which he transitioned to cephalexin. A renal biopsy was suggestive of minimal change disease as the etiology of his NS, which was later determined to be steroid-resistant.

Discussion

Children with NS are at risk for infection in part secondary to the disease process itself and in part due to therapeutic use of immunocompromising agents [1]. A study of 370 hospitalized children with NS found that infection was present in 40 % of patients, most often peritonitis and bacteremia, and less often cellulitis [2].

There are few case reports of *E. coli* cellulitis in children with NS apart from our own [3,4]. Unlike prior cases, which featured children with relapsed NS, our patient had a new diagnosis of NS with development of cellulitis occurring within 5 days of starting steroid therapy. Interestingly, *E. coli* cellulitis occurred in the proximal lower extremities in each of these cases.

Traditional teaching holds that most cases of cellulitis are due to beta-hemolytic streptococci and *Staphylococcus aureus*; however, a definitive bacteriologic etiology is often difficult to determine, and most patients are treated empirically [5]. Gram-negative rods, including *E. coli*, are an uncommon cause of cellulitis, more often seen in immunocompromised patients. Of note, a systematic review of bacteremia in the presence of cellulitis found that gram-negative isolates occurred more frequently than *S. aureus*, although

the data was not sufficient to determine how many cases occurred in the setting of immunocompromise [6].

Immune system dysfunction in NS is multifactorial. First, NS is defined by significant proteinuria, which includes loss of immunoglobulins and proteins essential to the complement system. There is evidence that loss of proteins, such as serum factor B, leads to impairment of the alternative complement pathway, which in turn may increase susceptibility to infection by encapsulated or gram-negative organisms, including *E. coli* [7]. Corticosteroids may also contribute to the immune system dysfunction seen in NS. Glucocorticoids may cause immune dysfunction via inhibition of neutrophil-endothelial adhesion, reduced phagocytosis of opsonized bacteria by the reticulo-endothelial system, and slight reductions in IgA and IgG levels. Of note, the time course of immune system dysfunction appears to be variable with neutrophils being affected within hours and immunoglobulin reduction within 2–3 weeks [8]. This study also demonstrated a lack of antibody response in steroid-resistant NS. Nevertheless, the relative amount that steroids versus proteinuria contributes to immune system dysfunction in patients with NS is unclear. Our case suggests that the effects of both the underlying pathophysiology of NS and corticosteroid treatment may be additive or synergistic in their suppression of the body's immune response to bacteria.

Last, our case highlights the diagnostic challenges inherent in evaluating and treating nonverbal children with ASD. Our patient's initial chief concerns were seizure and gait disturbance, which in isolation might suggest central nervous system pathology; however, a thorough examination revealed an underlying rash, leading to an infectious work-up. An acute change in behavior from baseline in these patients should always prompt the physician to perform a comprehensive history and examination, and to consider additional work-up for conditions such as constipation, dental caries, urinary tract infections, non-accidental trauma, and dermatologic conditions, among others [9,10].

Conclusion

In conclusion, we present a case of a medically complex child with new-onset NS who presented with *E. coli* bacteremia and cellulitis within days of initiation of systemic steroids. This case demonstrates how NS may predispose patients to bacterial infections of atypical etiologies because of the immunosuppressive

effects of NS itself and its empiric treatment with corticosteroids. Additionally, we highlight the diagnostic challenges of evaluation and management of a nonverbal patient with ASD whose chief concern was not necessarily suggestive of his underlying problem.

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Informed consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Cristina E. Alcorta, MD – writing, review, and editing
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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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